Clostridium difficile infection in patients with inflammatory bowel disease : a case control study

Vitikainen, Krista

2018

Vitikainen , K , Haapamaki , J , Farkkila , M , Anttila , V-J & Arkkila , P 2018 , ' Clostridium difficile infection in patients with inflammatory bowel disease : a case control study ' , Scandinavian Journal of Gastroenterology , vol. 53 , no. 8 , pp. 947-951 . https://doi.org/10.1080/00365521.2018.149

http://hdl.handle.net/10138/305915
https://doi.org/10.1080/00365521.2018.1492012

unspecified
publishedVersion

Scandinavian Journal of Gastroenterology

ISSN: 0036-5521 (Print) 1502-7708 (Online) Journal homepage: http://www.tandfonline.com/loi/igas20

Clostridium difficile infection in patients with inflammatory bowel disease: a case control study

Krista Vitikainen, Johanna Haapamäki, Martti Färkkilä, Veli-Jukka Anttila & Perttu Arkkila

To cite this article: Krista Vitikainen, Johanna Haapamäki, Martti Färkkilä, Veli-Jukka Anttila & Perttu Arkkila (2018) *Clostridium difficile* infection in patients with inflammatory bowel disease: a case control study, Scandinavian Journal of Gastroenterology, 53:8, 947-951, DOI: 10.1080/00365521.2018.1492012

To link to this article: https://doi.org/10.1080/00365521.2018.1492012

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
2018, VOL. 53, NO. 8, 947–951
https://doi.org/10.1080/00365521.2018.1492012

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Clostridium difficile infection in patients with inflammatory bowel disease: a case control study

Krista Vitikainen[a], Johanna Haapamäki[a], Martti Färkkilä[a], Veli-Jukka Anttila[b] and Perttu Arkkila[a]

[a]Department of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland; [b]Department of Infectious Diseases, Helsinki University Central Hospital, Helsinki, Finland

ABSTRACT

Objective: Characterization of predisposing factors for *Clostridium difficile* infection recurrence (rCDI) and outcome in inflammatory bowel disease (IBD) patients.

Methods: Clinical characteristics of 167 inflammatory bowel disease patients with *Clostridium difficile* infection (IBD-CDI cohort) treated in Helsinki University Central Hospital were gathered. Medical history of the last three months preceding a toxin positive CDI test was recorded. Parameters, including ribotype of *C. difficile*, mortality and recurrence were compared with age and gender-matched *C. difficile* patients (CDI cohort).

Results: No difference was found in rCDI between IBD-CDI and CDI cohorts. As compared with IBD subtypes, rCDI was least common among patients with Crohn's disease. The use of immunosuppressant therapy was higher in IBD patients with two or more CDI episodes. *C. difficile* ribotype 027 increased the rates for rCDI in IBD patients but not in non-IBD-CDI patients. The prevalence of 027 ribotype and mortality rates did not differ significantly among the cohorts. None of the IBD patients underwent colectomy upon CDI.

Conclusion: IBD patients are not more susceptible for rCDI than non-IBD patients. Predisposing factors for rCDI among IBD patients are associated with immunosuppressant treatments, colon affecting IBD and CDI caused by ribotype 027. CDI does not worsen the prognosis of IBD patients.

ARTICLE HISTORY
Received 3 May 2018
Revised 17 June 2018
Accepted 18 June 2018

KEYWORDS
Inflammatory bowel disease; ulcerative colitis; Crohn's disease; *Clostridium difficile* infection; recurrence of *C. difficile* infection

Introduction

Clostridium difficile infection (CDI) is the most common cause of antibiotic-associated diarrhea, especially among hospitalized patients. Clinical manifestations of CDI range from asymptomatic carriage to severe fulminant colitis and death. Dismal prognosis is associated especially with a hypervirulent strain of *C. difficile* (NAP1/B1/027). The 027-ribotype of *C. difficile* is characterized by increased disease acitivty and transmissibility [1].

CDI is classically considered a nosocomial concern but the prevalence of infection in community has increased worldwide, especially in certain patient groups. Patients with inflammatory bowel disease (IBD) are one of the patient groups among the incidence of CDI has increased over the past few decades, especially in the industrialized countries [2,3]. IBD patients have shown to be more susceptible to develop CDI with more severe outcomes, such as colectomies and mortality, than non-IBD-CDI patients [4,5]. In addition to disease susceptibility, IBD patients are documented to have 33% higher risk to develop recurrence of CDI compared with non-IBD patients with CDI [6].

Currently, the predisposing factors for CDI in IBD patients have been studied widely in recent studies, while risk factors for rCDI remain poorly established. Conventional risk factors for CDI in the general population include advanced age, chemotherapy, co-morbidities, prolonged hospitalization and use of certain drugs, most notably antibiotics and proton pump inhibitors (PPIs) [7–9]. In IBD, both Crohn's disease (CD) and ulcerative colitis (UC) patients are at high-risk for CDI, although patients with UC have been reported to be more susceptible to CDI than CD patients [10–12]. IBD-associated treatment factors, such as use of immunosuppressants, have also been suggested to increase the risk for CDI. Compared with other immunosuppressive agents, use of corticosteroids has shown a threefold increase in the rates of CDI in IBD patients [13,14]. Antibiotics in turn, do not seem to play a critical role in triggering CDI in these patients [15]. Factors that increase the risk for rCDI in IBD patients are related with 5-aminosalicylic acid (5-ASA), steroids, antibiotics, biologic therapy and IBD that affects colon [6]. To our knowledge, the prevalence of *C. difficile* BI/NAPI/027 ribotype and its effect on recurrent infections in IBD patients have not been investigated previously.

This is a comprehensive regional study of IBD-CDI and CDI patients in the southern of Finland. Our study focused on the differences between clinical characteristics of IBD and CDI patients. We compared IBD patients with CDI to CDI patients without IBD to determine predisposing factors to rCDI. We analyzed IBD-CDI and CDI patients' prognosis in general in a vast study cohort while many previous studies have processed prognosis more concisely with smaller study cohorts or only by the risk of colectomy [4].

CONTACT Krista Vitikainen krista.vitikainen@helsinki.fi Department of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland

Material and methods

In this retrospective cohort study, 167 IBD patients with CDI were enrolled from medical records of Helsinki University Hospital (HUH) register. The medical records are from 2008 to 2013. The data from records were collected between June and July in 2016. Following variant forms of IBD were included in our study: UC ($n = 105$, 62.9%), CD ($n = 48$, 28.7%) and unspecified IBD (IBD-U/indeterminate colitis, $n = 14$, 8.4%). Diagnosis of IBD was done according to standard clinical, endoscopic, radiological and histologic criteria. The study was approved by the institutional review board of Helsinki University Hospital.

Clinical parameters including CDI episodes and exposure to commonly used medications were collected from IBD-CDI patients' medical records. Usage of IBD-related drugs, antibiotics, NSAIDs and PPIs during the last three months before a toxin positive CDI test were recorded. No exclusion criteria were used in the study and possible comorbidities in either of the cohorts were ignored. For mortality analyzes, death for any cause within 30 days after established CDI diagnosis was recorded.

In Southern Finland, three step diagnostic methods for detection of CDI are used since the year of 2008: *C. difficile* cytotoxin assay and stool culture to isolate *C. difficile* with subsequent cytotoxin assay, if direct cytotoxin assay was negative; and if the culture was positive, 027 was tested by the multiplex PCR method published elsewhere [16]. These tests are performed for IBD patients, who are symptomatic after antibiotics and for patients with IBD exacerbation.

Recurrence of CDI is defined as recurrent of diarrhea with a positive stool test at least 14 days after the initial episode of symptomatic CDI.

Age- and gender-matched control group including non-IBD-related CDI patients (CDI cohort) was gathered from HUH register to compare the characteristics of patients in IBD-CDI cohort.

Statistical methods

Patient characteristics between groups were analyzed using the chi-square test, the Fisher exact test and the Bonferroni multiple comparison test. One-way analysis of variance was used for continuous variables. A p value of $<.05$ was considered statistically significant. All calculations were accomplished with NCSS-2000 software (Kaysville, UT, USA).

Results

Patient characteristics

A total of 167 IBD patients with CDI were included in our IBD-related CDI (IBD-CDI) study cohort with variable number of CDI episodes. Patient characteristics of both cohorts are represented in Table 1. The mean age in IBD-CDI cohort was 46.1 (range 6.4–91.9 years).

Recurrence of CDI

The overall count of CDI episodes is shown in Table 1. The number of recurrences in rCDI was between two to five (mean+/–SD 1.54+/–0,97) and two to seven (mean+/–SD 1.52+/–1,08) episodes in the IBD-CDI and CDI cohort, respectively.

No significant difference in recurrence rate was evident between IBD-CDI and CDI cohorts ($p = .551$). A total of 128 (IBD-CDI) and 126 (CDI) episodes occurred among men ($p = .663$), 129 (IBD-CDI) and 123 (CDI) among females ($p = .216$). Within the IBD-CDI cohort alone rCDI seemed to occur more frequently among females than among men, although statistical significance was not found. Comparing rCDI between IBD subtypes, the recurrence of CDI was most infrequent in patients with CD (Figure 1). CDI episodes (%) in non-IBD-CDI cohort are shown in Figure 2.

Table 1. Characteristics of the patients.

		IBD-CDI $n = 167$	CDI without IBD $n = 164$
Age	(Average ± SD) yrs	46.1 ± 21.0	42.9 ± 20.2
Gender	Males *n* (%)	85 (50.9)	83 (50.6)
	Females *n* (%)	82 (49.1)	81 (49.4)
IBD subtypes	CD *n* (%)	48 (28.7)	NA
	UC *n* (%)	105 (62.9)	NA
	IBD-U *n* (%)	14 (8.4)	NA
CDI episodes	One (%)	116 (69.5)	120 (73.2)
	Two (%)	26 (15.6)	23 (14.0)
	Three or more (%)	25 (15.0)	21 (12.8)
Ribotype	027 (%)	4 (2.4)	11 (6.7)
	Other (%)	160 (95.8)	149 (90.9)
	NA (%)	3 (1.8)	

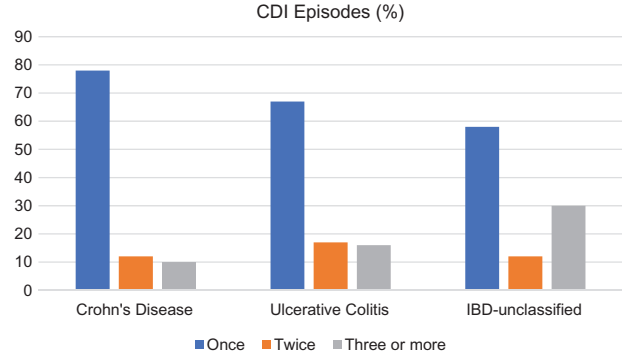

Figure 1. *Clostridium difficile* episodes (%) in variant forms of IBD patients.

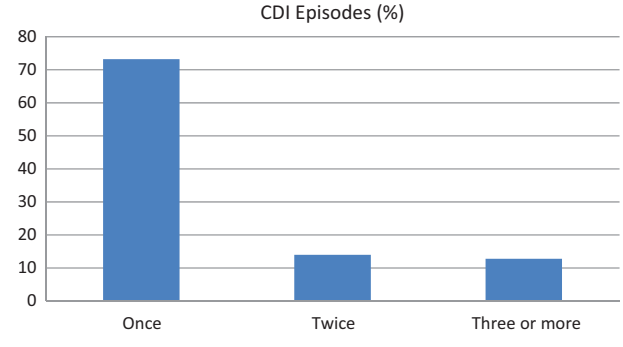

Figure 2. *Clostridium difficile* episodes (%) in non-IBD-CDI patients.

Drug usage in the IBD-CDI cohort was recorded for three months preceding CDI episode for available cases (Table 2). Corticosteroids and 5-ASA were the most commonly used medication in the IBD-CDI cohort. Over half of the patients had been exposed to 5-ASA or systemic corticosteroid and a few to local corticosteroid before CDI episode. Proportionally the usage of both systemic corticosteroid and 5-ASA was higher in patients with two or more CDI episodes, although statistical significance was not reached. Patients with no corticosteroid or 5-ASA-intake were not as susceptible to have a recurrent infection. Other medications in our study did not appear to have a similar impact on the rate of recurrence of CDI within the IBD-CDI cohort.

Patients in IBD-CDI cohort had also frequently received antibiotic therapy during the previous three months before a CDI episode: 73.4% of all IBD-CDI patients were exposed to antibiotics (34/40 of CD patients, 73/105 of UC patients and 9/13 of IBD-U patients, unknown from 9 IBD-CDI patients). Especially the use of broad spectrum antibiotics seemed to be common in IBD patients before the CDI diagnosis. No significant difference was found in different antibiotics and different IBD types.

C. difficile strains

To examine differences in *C. difficile* ribotypes between IBD and non-IBD-related CDI patients, we evaluated the prevalence of 027 ribotype between these cohorts. Ribotype 027 represented a minority of CDI in both the cohorts with a slightly higher prevalence in non-IBD-related CDI cases, but no statistical significant difference was found ($p = .101$). We also compared the effect of *C. difficile* ribotype 027 to recurrent infections in both the cohorts. The risk for rCDI was higher in IBD patients with CDI caused by ribotype 027 as compared with non-IBD-CDI patients. In IBD cohort CDI episodes according to ribotype 027 status were as follows: 1/116 non-recurrent CDI caused by ribotype 027 vs. 3/48 recurrent infection caused by ribotype 027, 115/116 non-recurrent CDI caused by other ribotype than 027 vs. 45/48 recurrent CDI caused by other ribotype than 027 ($p = .041$).

Table 2. CDI episodes in IBD patients using different treatments.

	Once users % (*n*/data obtained)	Twice users % (*n*/data obtained)	Three or more episodes users % (*n*/data obtained)
5-ASA	65,8% (73/111)	73,1% (19/26)	75,0% (18/24)
Corticosteroids			
Systemic	52,3% (57/109)	56,0% (14/25)	58,3% (14/24)
Local	5,5% (6/109)	8,0% (2/25)	8,3% (2/24)
Both	5,5% (6/109)	20,0% (5/25)	4,2% (1/24)
Thiopurines	36,4% (40/110)	38,5% (10/26)	29,2% (7/24)
Infliximab	12,7% (14/110)	11,5% (3/26)	4,2% (1/24)
Adalimumab	3,6% (4/110)	0/26	0/24
Vedolizumab	0/110	0/26	0/24
Antibiotics	75,0% (81/108)	68,0% (17/25)	75,0% (18/24)
NSAIDs[a]	28,2% (31/110)	15,4% (4/26)	25,0% (6/24)
PPIs[b]	47,3% (52/110)	53,8% (14/26)	45,8% (11/24)

[a]Nonsteroidal anti-inflammatory drugs.
[b]Proton pump inhibitors. No statistically significant differences were found. Vedolizumab and adalimumab were not used in our cohort.

Prognosis

We wanted to clarify the effect of CDI on IBD patients' mortality. When comparing the rates of 30-day mortality after CDI episode between genders in the IBD-CDI and CDI cohorts, we identified a difference in CDI-related mortality among men: 1.2% of IBD-CDI and 7.4% of CDI patients succumbed during 30 days after CDI diagnosis ($p = .046$). Mortality rates did not differ among females (IBD-CDI vs. CDI patients, 2.4% vs. 2.5%, $p = .970$).

In general, IBD-CDI patients also had lower mortality rates compared to CDI patients. Two-day mortality rates were none vs. 1 (0.6%) in IBD-CDI and CDI patients, seven-day mortality rates 1 (0.6%) vs. 4 (2.5%) and 30-day mortality rates 3 (1.8%) vs. 8 (5.0%), respectively. Altogether, short-term survival (30 days post-infection) after CDI episode was 98.2% in IBD-related CDI and 95.0% in non-IBD-related CDI ($p = .108$).

We also wanted to evaluate IBD-CDI patients' risk to undergo colectomy. In our study, none of the IBD patients underwent surgery after CDI.

Discussion

IBD Patients are at increased risk for developing symptomatic CDI with worse clinical outcomes as compared with the general population. IBD patients are also more susceptible to have recurrences of CDI. Predisposing factors for CDI in IBD patients have been widely covered in recent studies, while the risk for rCDI in IBD patients has not garnered much attention. The present study evaluated which are the predisposing factors for rCDI in IBD patients. The most important risk factor for rCDI seems to be the use of systemic corticosteroid. Moreover, higher 5-ASA-intake was associated with two or more CDI episodes. However, the prevalence of rCDI, 027 ribotype and mortality is not higher in IBD-CDI compared to non-IBD-CDI patients. None of the IBD patients underwent colectomy after CDI. CDI caused by ribotype 027 increases the risk for rCDI in IBD patients.

The incidence of CDI has been increasing during the twenty-first century. It is the most common cause of antibiotic-associated diarrhea, especially among the hospitalized. CDI is classically considered a nosocomial concern but the incidence is also detected to be higher in non-hospitalized patients with IBD [10,17]. The increased incidence of CDI is also coupled with higher risk of recurrence among IBD patients. CDI recurrences have been shown to occur 33% more frequently among IBD patients as compared to non-IBD-CDI patients [6]. In our study cohort, there was no difference in the rates of rCDI between IBD and non-IBD-related CDI patients.

Differences in the rates of rCDI between IBD subtypes have also been established [18,19]. UC and non-ileal CD patients have been reported not only to have a higher prevalence of CDI but also increased risk for recurrent infections [6,11]. Our study recorded least rCDI episodes in CD patients. Recurrences of CDI were frequently seen in other forms of IBD (UC and IBD-U). The greater prevalence of CDI

and its recurrent infections may be due to the manifestation of the disease which in these variant forms is limited to the colon, where the *C. difficile* bacterium colonizes, in contrast to CD which can affect any parts of the gastrointestinal tract. Hypothetically, one would expect that a colon-manifesting process could set up the premises for CDI colonization, which could explain the greater prevalence of recurrent infections in other forms of IBD.

Currently, predisposing pharmacological and disease associated factors for rCDI in IBD patients are only poorly established. Certain drugs such as corticosteroids, 5-ASA, biologics and antibiotics have been associated with rCDI in a smaller IBD cohort study [6].

Corticosteroids have been used as a conventional treatment of IBD due to its effectiveness in a rapid resolution of IBD symptoms. However, steroid usage has been shown to increase a risk to develop rCDI in patients with concomitant IBD [6]. Our study further highlights the impact of high corticosteroid-intake and incidence of rCDI in IBD patients. In our IBD-CDI cohort as much as 61.4% of all patients had used systemic corticosteroids during the previous three months preceding a CDI. Moreover, the intake of corticosteroids was further enriched in patients with CDI recurrences. However, since corticosteroids are conventionally given to IBD patients with an IBD exacerbation, it is also possible that the flare ups could have an effect on developing a recurrence infection independent of steroid exposure. For clinicians it can cause confusion whether to decrease or increase the dose of immunosuppressant in IBD patients with CDI. However, according to the latest research, when the diagnosis of CDI is confirmed, initiation of immunosuppressive agents may be considered after 48–72 h when targeted antibiotics for CDI in IBD patients are given [20].

5-ASA has been used as an anti-inflammatory drug for induction and maintenance of remission in IBD patients and has also been associated with rCDI [6]. Many of IBD-CDI patients in our study cohort had received 5-ASA preceding CDI episode. Moreover, within IBD-CDI cohort 5-ASA usage was more common among patients with two or more CDI episodes. It has been hypothesized that the intake of 5-ASA could develop dysbiosis which alone or co-operatively with colon affecting IBD could make the patients more susceptible to CDI and its recurrent episodes [21,22].

Antibiotics do not seem to play a critical role in triggering CDI in IBD patients [10,15]. As compared to nosocomial CDI, IBD-related infection appears to occur in younger patients who have not received antibiotics recently. Antibiotic exposure has found to occur only in 40–60% of IBD patients with subsequent CDI [23,24]. However, in IBD patients antibiotics have been associated with rCDI [6]. In our study cohort, majority of the IBD patients (73.4%) were exposed to antibiotics in the past three months before CDI diagnosis. While almost all antibiotics have been associated with CDI-related diarrhea in general, the most common association has been noticed to be with only certain antibiotics, including fluoroquinolones, which are commonly used in IBD [25]. Thus, some of the same antibiotics which most often cause CDI-related diarrhea are used as a treatment in IBD patients who already have increased risk to develop CDI. This is an indication for careful consideration when to start antibiotics for IBD patients.

The prevalence of *C. difficile* ribotype 027 has not been thoroughly investigated among patients with IBD. In the general population, the hypervirulent form of *C. difficile* has been associated with more severe disease and dismal outcome [1]. In our study, ribotype 027 represented minority of CDI cases in both the cohorts and the prevalence did not differ significantly between IBD-CDI ad CDI patients. However, ribotype 027 seems to increase the risk for rCDI in IBD patients.

Previous studies have been considering the effects of CDI in IBD patient outcomes, such as in mortality and colectomy. They have shown mortality rates to be twice higher in IBD patients with CDI as compared to non-IBD patients with CDI and even four-fold higher than in an inpatient with IBD alone [11,26]. In our study, significant difference between these two groups in general was not noticed. IBD-CDI patients seem to have even less mortality compared to non-IBD-CDI patients. This favorable mortality rate among IBD-related cases may arise due to lack of traditional risk factors, including other co-morbidities in comparison to non-IBD-related CDI. In fact, IBD may often be the only underlying disease in these CDI cases. Moreover, the risk of colectomy was not either elevated in our IBD-CDI cohort, while none of the IBD-CDI patient underwent colectomy upon infection.

Here, we have gathered and analyzed a retrospective cohort of Finnish IBD patients with CDI and compared patient characteristics, risk factors and CDI recurrence with non-IBD-related CDI patients. Our study complements previous studies and provides a more insight into the poorly characterized CDI recurrence, rate and prognosis among IBD patients. The strength of our study is a large IBD-CDI cohort and *C. difficile* ribotype 027 analyzation. The weakness of our study was ignorance of disease activity in the IBD-CDI cohort. At the moment, diagnosis of CDI in IBD patients may be difficult due to overlapping clinical symptoms of CDI and IBD flare up. Clinicians should accurately document each case with rapid diagnosis and subsequent adequate therapy. Routine stool sample screening for CDI in each case with characteristics of IBD exacerbation or infectious colitis is recommended before giving any antibiotics.

Conclusions

According to our research, the most important risk factor for rCDI was systemic corticosteroid usage. Moreover, higher 5-ASA and corticosteroid-intake was associated with two or more CDI episodes. We identified no significant difference in the prevalence of rCDI, ribotype 027 and mortality between IBD-CDI and CDI cohorts. CDI caused by ribotype 027 increases the risk for rCDI in IBD patients. CDI seems not to increase the risk for colectomies in IBD patients after CDI episode. More prospective studies are required to evaluate clearly different risk factors for CDI in IBD patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The study was granted by the EVO-grant of Helsinki University Central Hospital and supported by State funding for University-Level Health Research.

ORCID

Martti Färkkilä http://orcid.org/0000-0002-0250-8559

References

[1] Lewis SS, Anderson DJ. Treatment of *Clostridium difficile* infection: recent trial results. Clin Investig (Lond). 2013;3:875–886.
[2] Molodecky NA. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.
[3] Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. Inflamm Bowel Dis. 2006;12(Suppl 1):S3–S9.
[4] Law CCY, Tariq R, Khanna S, et al. Systematic review with meta-analysis: the impact of *Clostridium difficile* infection on the short- and long-term risks of colectomy in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;45(8):1011–1020.
[5] Nguyen GC, Kaplan GG, Harris ML, et al. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103(6):1443–1450.
[6] Razik R, Rumman A, Bahreini Z, et al. Recurrence of *Clostridium difficile* infection in patients with inflammatory bowel disease: the RECIDIVISM study. Am J Gastroenterol. 2016;111(8):1141–1146.
[7] Aseeri M, Schroeder T, Kramer J, et al. Gastric acid suppression by proton pump inhibitors as a risk factor for *Clostridium difficile*-associated diarrhea in hospitalized patients. Am J Gastroenterol. 2008;103(9):2308–2313.
[8] Janarthanan S, Ditah I, Adler DG, et al. *Clostridium difficile*-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107(7):1001–1010.
[9] Bloomfield LE, Riley TV. Epidemiology and risk factors for community-associated *Clostridium difficile* infection: a narrative review. Infect Dis Ther. 2016;5(3):231–251.
[10] Issa M, Vijayapal A, Graham MB, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):345–351.
[11] Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. Gut. 2008;57(2):205–210.
[12] Micic D, Yarur A, Gonsalves A, et al. Risk factors for *Clostridium difficile* isolation in inflammatory bowel disease: a prospective study. Dig Dis Sci. 2018;63(4):1016–1024.
[13] Schneeweiss S, Korzenik J, Solomon DH, et al. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther. 2009;30(3):253–264.
[14] Das R, Feuerstadt P, Brandt LJ. Glucocorticoids are associated with increased risk of short-term mortality in hospitalized patients with *Clostridium difficile*-associated disease. Am J Gastroenterol. 2010;105(9):2040–2049.
[15] Berg AM, Kelly CP, Farraye FA. *Clostridium difficile* infection in the inflammatory bowel disease patient. Inflamm Bowel Dis. 2013;19(1):194–204.
[16] Antikainen J, Pasanen T, Mero S, et al. Detection of virulence genes of *Clostridium difficile* by multiplex PCR. APMIS. 2009;117(8):607–613.
[17] Clayton EM, Rea MC, Shanahan F, et al. The vexed relationship between *Clostridium difficile* and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. Am J Gastroenterol. 2009;104(5):1162–1169.
[18] Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5(3):339–344.
[19] Khanna S, Shin A, Kelly CP. Management of *Clostridium difficile* infection in inflammatory bowel disease: expert review from the clinical practice updates committee of the AGA institute. Clin Gastroenterol Hepatol. 2017;15(2):166–174.
[20] D'Aoust J, Battat R, Bessissow T. Management of inflammatory bowel disease with *Clostridium difficile* infection. World J Gastroenterol. 2017;23(27):4986–5003.
[21] Liu F. Azathioprine, mercaptopurine, and 5-aminosalicylic acid affect the growth of IBD-associated campylobacter species and other enteric microbes. Front Microbiol. 2017;8:527.
[22] Andrews CN, Griffiths TA, Kaufman J, et al. Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2011;34(3):374–383.
[23] Bossuyt P, Verhaegen J, Van Assche G, et al. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. J Crohns Colitis. 2009;3(1):4–7.
[24] Fu N, Wong T. *Clostridium difficile* infection in patients with inflammatory bowel disease. Curr Infect Dis Rep. 2016;18(6):19.
[25] Pepin J, Saheb N, Coulombe M-A, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. 2005;41(9):1254–1260.
[26] Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis. 2013;7(2):107–112.